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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/652,622	08/29/2003	Yawei Ni	04137.0003U3	1025

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EXAMINER	
SCHNIZER, RICHARD A	
ART UNIT	**PAPER NUMBER**
1635	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/652,622	NI ET AL.	
	Examiner	Art Unit	
	Richard Schnizer, Ph. D.	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *04 May 2007*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,2,9-31,33,35-41,53,55-62,65-71 and 74-112* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1, 2, 9-31, 33, 35-41, 53, 55-62, 65-71, and 74-112* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

An amendment was received and entered on 5/4/07.

Claims 6-8, 32, 34, 42, 43, 47-52, 54, 72, and 73 were cancelled.

Claims 1, 2, 9-31, 33, 35-41, 53, 55-62, 65-71, and 74-112 remain pending and are under consideration in this Office Action.

This application is a continuation in part of 09/795,897, now US 6,777,000. However, the instant claims require a powder comprising nanoparticles or microparticles that can pass through a sieve having an opening size of about 250 microns in diameter. US 6,777,000 does not support this limitation, so the effective filing date of the instant claims is considered to be 8/29/03.

Rejections not reiterated from the previous action are withdrawn.

Claim Objections

Claims 1, 30, and 111 are objected to because they use an improper Markush format. Claims 1 and 111 recite "one or more physiologically active agents selected from the group consisting of", and then list a series of agents wherein the final two agents in the series are separated by the conjunction "or" instead of the conjunction "and". This makes it unclear which of the recited agents is a member of the group, and which is not. Claim 30 is objected to because the final and penultimate members of the recited Markush group are not separated by a conjunction (and).

Claim 53 is objected to because a portion of it is not double spaced.

Claim 50 is also ungrammatical because it recites "an particle".

Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claim 18 is rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claim 1 has been amended to require a physiologically active agent selected from the group consisting of peptides, proteins, vaccines comprising one or more antigens, live cells, dead cells in whole or in part, or viruses in whole or in part. Claim 18 depends from claim 1 and requires a physiologically active agent selected from a group that includes "a lipid", and "a nucleic acid". After the amendment to claim 1, it seems clear that the lipid or nucleic acid of claim 18 must now come from either the dead cell in part, or the virus in whole or in part of claim 1. However, the specification as filed does not disclose these subgenuses of lipids and nucleic acids. Instead, the terms "lipids" and "nucleic acids" are used only in the broadest sense without limitation to any specific subgenus. Accordingly one of skill in the art could not conclude that

Applicant contemplated these specific subgenuses, not fairly disclosed in the specification as filed, at the time the invention was made.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1, 2, 9-19, 22-24, 27-29, 33, 35-41, 53, 55-62, 65-68, 71, 74, 79-89, 92-106, and 108-110 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Baichwal et al (US Patent 5,612,053) in view of Watts et al (US 6,310,089) and Ni et al (US Patent 5,929,051).

Baichwal taught dry powdered compositions for controlled release of drugs by inhalation, and methods of use to deliver the drugs. See column 2, lines 40-45. The dry powdered compositions comprised polysaccharides such as alginates or carrageenans, as well as a cross linking agent such as divalent metal cations, e.g. calcium chloride. See abstract; and column 6, lines 16-24 and 44-59. In various embodiments, the size of the powder particles ranges from 0.1 to 10 microns, 2 to 10 microns, 63 to125 microns, and 45 to 355 microns. See column 5, lines 30-45. The composition can be prepared as a powder by dissolving a drug and polysaccharide particles, allowing them to contact each other in solution, drying the solution to form a solid, and milling to form particles of the appropriate size. See column 8, line 4 to column 9, line 67, especially column 8

lines 51-67, and column 9, lines 1-15 and 27-59. Absent evidence to the contrary, this results in contact between molecules of polysaccharide and molecules of drug, resulting in mixing on the molecular level. With regard to instant claim 2, note that the compositions can comprise more than one type of polysaccharide (column 5, lines 57-59). The compositions are delivered to regions of the body comprising fluids such as the respiratory tract (see column 5, lines 45-52). The drug can be any of a wide variety of drugs including polypeptides and peptides, see column 10, lines 1-8 and 62-65. Pharmaceutically acceptable excipients and fillers are included in the composition, see column 7, lines 16-55.

Baichwal did not teach a pectin.

Watts taught powders for inhalation comprising powdered polysaccharide microspheres including alginates and pectin, among others.

Ni taught that a calcium-induced gel-forming aloe pectin (AP 97-1) having a molecular eight of 1.36×10^6 Da, 91% (w/w) galacturonic acid, a degree of methylation of 4.4%, 10.3% (mole/mole) rhamnose, and 0.8% (mole/mole) 3-methoxy rhamnose, was suitable for the controlled release of a physiologically active agent to an animal. See column 5, lines 55-58, Table 10 at columns 19 and 20, column 27, lines 25-67, Figs. 5a-c, and Table 17 at columns 31 and 32. Ni also taught that the pectin was useful for delivering vaccines to mucosal surfaces of animals. See column 5, lines 55-58.

It would have been obvious to one of ordinary skill in the art at the tie of the invention to use a pectin as a polysaccharide in the invention of Baichwal, because it

was clear that pectins were routinely used in powdered compositions for inhalation at the time of the invention, as evidenced by Watts. MPEP 2144.06 indicates that when it is recognized in the art that elements of an invention can be substituted, one for the other, while retaining essential function, such elements are art-recognized equivalents. An express suggestion to substitute one equivalent component or process for another is not necessary to render such substitution obvious. In re Fout, 675 F.2d 297, 213 USPQ 532 (CCPA 1982). Furthermore, MPEP 2144.07 indicates that the selection of a known material based on its suitability for its intended use supports the determination of prima facie obviousness. See also Sinclair & Carroll Co. v. Interchemical Corp., 325 U.S. 327, 65 USPQ 297 (1945). In this case, it was clear to one of skill in the art that pectins and alginates could both be used in powdered microsphere form to deliver drugs by inhalation, so it would have been obvious to substitute one for the other in the method of Baichwal.

It would have been obvious to one of ordinary skill in the art at the time of the invention to use the pectin of Ni in the invention of Baichwal. One would have been motivated to do so because Ni taught that the pectin was suitable for controlled release of a physiologically active agent to an animal. MPEP 2144.07 indicates that the selection of a known material based on its suitability for its intended use supports the determination of prima facie obviousness.

Although Baichwal is silent as to whether or not the divalent metal cation is a solid phase that is distinct from the mixed polysaccharide and drug solid phase, the

inclusion of the divalent cation in this phase or its addition as a separate solid phase is considered to be a matter of design choice.

Regarding claims 29, 68, 71, and 106, requiring a thickener, the polysaccharide of Baichwal is considered to be a thickener. Note that the compositions can comprise more than one type of polysaccharide (column 5, lines 57-59), and that the polysaccharides can be present in a concentration of 10-50%, typically (column 8, lines 36 and 37). Claims 37-40 and 101 are included in this rejection because it is considered to read on a method in which the solid powder of Baichwal is administered to the lung or nasal passages, and then comes into contact with lung tissue or nasal tissue as a suspension in the extracellular or respiratory fluids. See e.g. column 5, lines 45-52.

Claims 20, 21, 75-78, 111, and 112 are rejected under 35 U.S.C. 103(a) as being unpatentable over Baichwal et al (US Patent 5,612,053), and Watts et al (US 6,310,089), and Ni et al (US Patent 5,929,051), as applied to claims 1, 2, 9-19, 22-24, 27-29, 33, 35-41, 53, 55-62, 65-68, 71, 74, 79-89, 92-106, and 108-110 above, and further in view of Kuo et al (US Patent 6,518,239).

The teachings of Baichwal, Watts, and Ni are discussed above and can be combined to render obvious compositions comprising a pectin, a drug, and divalent or multivalent metal cation, wherein the composition is in the form of a powder of particles less than 250 microns in diameter.

The cited references did not teach delivery of a vaccine.

Kuo taught delivery of vaccines by inhalation of dry powders comprising a vaccine.

It would have been obvious to one of ordinary skill in the art at the time of the invention to use the composition and method of Baichwal as modified by Watts and Ni to deliver a vaccine because it was clear to those of ordinary skill that the method of Baichwal could be used to deliver polypeptides by inhalation, and that polypeptide vaccines were routinely delivered by inhalation. Thus the invention as a whole was prima facie obvious.

Claims 25, 26, 90, and 91 are rejected under 35 U.S.C. 103(a) as being unpatentable over Baichwal et al (US Patent 5,612,053), and Watts et al (US 6,310,089), and Ni et al (US Patent 5,929,051), as applied to claims 1, 2, 9-19, 22-24, 27-29, 33, 35-41, 53, 55-62, 65-68, 71, 74, 79-89, 92-106, and 108-110, above, and further in view of Gordon et al (US Patent 2,629,665).

The teachings of Baichwal, Watts, and Ni are discussed above and can be combined to render obvious compositions comprising a pectin, a drug, and divalent or multivalent metal cation, wherein the composition is in the form of a powder of particles less than 250 microns in diameter.

The cited references did not teach the use of calcium phosphate.

Gordon taught that almost any calcium ion, including calcium chloride, mono-calcium phosphate, di-calcium phosphate, etc could be used to cause pectin to form a gel. See column 4, lines 6-15.

It would have been obvious to one of ordinary skill in the art at the time of the invention to use calcium phosphate in the invention of Baichwal, as modified by Watts and Ni. MPEP 2144.06 indicates that when it is recognized in the art that elements of an invention can be substituted, one for the other, while retaining essential function, such elements are art-recognized equivalents. An express suggestion to substitute one equivalent component or process for another is not necessary to render such substitution obvious. In re Fout, 675 F.2d 297, 213 USPQ 532 (CCPA 1982). In this case, it was well known in the art calcium phosphate could be substituted for the calcium chloride of Baichwal or Ni. Furthermore, MPEP 2144.07 indicates that the selection of a known material based on its suitability for its intended use supports the determination of prima facie obviousness.

Claims 30, 31, 69, 70, and 107 are over Baichwal et al (US Patent 5,612,053), and Watts et al (US 6,310,089), and Ni et al (US Patent 5,929,051), as applied to claims 1, 2, 9-19, 22-24, 27-29, 33, 35-41, 53, 55-62, 65-68, 71, 74, 79-89, 92-106, and 108-110, and further in view of Mizushima et al (US Patent 5,942,242).

The teachings of Baichwal, Watts, and Ni are discussed above and can be combined to render obvious compositions comprising a pectin, a drug, and divalent or multivalent metal cation, wherein the composition is in the form of a powder of particles less than 250 microns in diameter.

The cited references did not teach the thickeners recited in instant claims 30, 31, 69, 70, and 107.

Mizushima taught that hydroxypropylmethylcelluloses, carboxymethylcelluloses, carboxymethylchitin, polyvinylpyrrolidone, hyaluronic acid, gelatin, and dextran were useful additives to inhalable powders because they increased adherence to the nasal mucosa. See column 5, lines 13-34.

It would have been obvious to one of ordinary skill in the art at the time of the invention to use any of the agents taught by Mizushima in the composition of Baichwal as modified by Watts and Ni in order to improve the adherence of the composition upon nasal administration.

Response to Arguments

Applicant's arguments filed 5/4/07 have been fully considered but they are not persuasive.

Applicant addresses the obviousness rejections at pages 18-21 of the response.

Applicant argues that the claimed invention arises new and non-obvious combinations of previously known elements, and asserts that one of ordinary skill would have had to make multiple selections of elements from among Baichwal's many alternative disclosures to arrive at a formulation of a solid polysaccharide composition comprising a mixture of a polysaccharide gum and one of the biologically derived physiologically active agents recited in the instant claims, wherein the composition is formulated as a solid mixture of components rather than a physical composite of separate ingredients, and wherein the composition is not pre-gelled as formulated, and having appropriate particle sizes wherein the particles would form a gel in situ. This is unpersuasive because it is presented as an opinion and not supported by any evidence.

Baichwal clearly discloses dry powdered compositions for delivery by inhalation that can be milled to any appropriate size, and suggests a variety of sizes within the claimed range. It would be obvious to use the pectin of Ni in the invention of Baichwal for the reasons set forth in the rejection, and the ability to form a gel in situ would be an inherent characteristic of the resulting composition. The use of thickeners in inhalable powders is obvious and routine because they increase adherence to the nasal mucosa, as disclosed in Mizushima.

Applicant further contends that the claimed compositions exhibit unexpected advantages and overcome previously unsolved problems. Applicant asserts that many biologically active agents are typically formulated as liquids that require cold storage, but that the instant compositions stabilize such agents in dry form, referring to page 23 of the specification. This is unpersuasive because Applicant has presented no evidence that the dry powdered compositions of Baichwal would not also provide similar stabilization, and because page 23 of the instant specification does not refer to any such stabilization. At page 24, the specification refers to unexpectedly stabilization and storage of biological agents, but provides no evidence in support, such that it is unclear if the stabilization is of practical and statistical significance and it is unclear if the unexpected effect is achieved with all of the claimed compositions such that the claims are commensurate in scope with the unexpected effect. See MPEP 716.02(b and d).

Applicant also argues that the claimed compositions unexpectedly overcome the art recognized problem of rapid clearance of biological agents from nasal mucosa due to the characteristic in situ gelling of the claimed compositions. This is does not

overcome the obviousness rejection because Applicant has provided no evidence that the dry compositions of Baichwal which absorb water and form gels (column 8, lines 22-25) would not do so on contact with mucosal surfaces, thus overcoming the problem of rapid clearance even without the use of the pectin of Ni. In other words it appears that the solution to the art recognized problem was already apparent in the prior art, and therefore not unexpected.

Applicant argues that Example 29 presents unexpected results. This is unpersuasive because the example involves delivery of naked antigen compared to delivery of naked antigen and aloe pectin, and does not compare the claimed invention with delivery of an antigen and another polysaccharide such as alginate or carrageenan. Accordingly, it is unclear if the results were unexpectedly superior to those which would have been obtained with polysaccharide-containing compositions that were obvious or anticipated by the prior art (e.g. Baichwal et al (US Patent 5,612,053) in view of Kuo et al (US Patent 6,518,239) see pages 7 and 8 of the Action mailed 10/30/06.

For these reasons the rejections are considered proper and are maintained.

Conclusion

No claim is allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner(s) should be directed to Richard Schnizer, whose telephone number is 571-272-0762. The examiner can normally be reached Monday through Friday between the hours of 6:00 AM and 3:30 PM. The examiner is off on alternate Fridays, but is sometimes in the office anyway.

If attempts to reach the examiner by telephone are unsuccessful, the Examiner's supervisor, J. Douglas Schultz, can be reached at (571) 272-0763. The official central fax number is 571-273-8300. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

Patent applicants with problems or questions regarding electronic images that can be viewed in the Patent Application Information Retrieval system (PAIR) can now contact the USPTO's Patent Electronic Business Center (Patent EBC) for assistance. Representatives are available to answer your questions daily from 6 am to midnight (EST). The toll free number is (866) 217-9197. When calling please have your application serial or patent number, the type of document you are having an image problem with, the number of pages and the specific nature of the problem. The Patent Electronic Business Center will notify applicants of the resolution of the problem within 5-7 business days. Applicants can also check PAIR to confirm that the problem has been corrected. The USPTO's Patent Electronic Business Center is a complete service center supporting all patent business on the Internet. The USPTO's PAIR system provides Internet-based access to patent application status and history information. It also enables applicants to view the scanned images of their own application file folder(s) as well as general patent information available to the public.

For all other customer support, please call the USPTO Call Center (UCC) at 800-786-9199.

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